0-09-P

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA-477]

Schedules of Controlled Substances: Placement of Zipeprol in Schedule I

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Final rule.

SUMMARY: With the issuance of this final rule, the Drug Enforcement Administration places zipeprol (chemical name: 1-methoxy-3-[4-(2-methoxy-2-phenylethyl)piperazin-1-yl]-1-phenylpropan-2-ol), including its isomers, esters, ethers, salts, and salts of isomers, esters and ethers, whenever the existence of such isomers, esters, ethers and salts is possible within the specific chemical designation, in schedule I of the Controlled Substances Act. This action is being taken to enable the United States to meet its obligations under the 1971 Convention on Psychotropic Substances. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle zipeprol.

DATES: Effective [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT: Dr. Terrence L. Boos, Drug and Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362-3249.

SUPPLEMENTARY INFORMATION:

Legal Authority

The United States is a party to the 1971 United Nations Convention on Psychotropic Substances (1971 Convention), February 21, 1971, 32 U.S.T. 543, 1019 U.N.T.S. 175, as amended. Procedures respecting changes in drug schedules under the 1971 Convention are governed domestically by 21 U.S.C. 811(d)(2) - (4). When the United States receives notification of a scheduling decision pursuant to Article 2 of the 1971 Convention adding a drug or other substance to a specific schedule, the Secretary of the Department of Health and Human Services (HHS),[1] after consultation with the Attorney General, shall first determine whether existing legal controls under subchapter I of the Controlled Substances Act (CSA) and the Federal Food, Drug, and Cosmetic Act meet the requirements of the schedule specified in the notification with respect to the specific drug or substance.[2] Based on those determinations, as appropriate, the Secretary of HHS (Secretary) shall recommend to the Attorney General that he initiate proceedings for scheduling the drug or substance pursuant to 21 U.S.C. 811(a) and (b).[3] The CSA also stipulates that in certain circumstances where the permanent section 811(a) scheduling will not be completed in time as required by the 1971 Convention, the Attorney General shall, after satisfying other specified conditions, issue a temporary order controlling the drug or substance under schedule IV or V, whichever is most appropriate to carry out the minimum United States obligations under the 1971 Convention.[4]

In the event that the Secretary did not so consult with the Attorney General to make a determination about the existing legal controls, and the Attorney General did not issue a temporary order, the procedures for permanent scheduling are set forth in 21

---

[1] As discussed in a memorandum of understanding entered into by the Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), FDA acts as the lead agency within HHS in carrying out the Secretary's scheduling responsibilities under the CSA, with the concurrence of NIDA. 50 FR 9518 (March 8, 1985). The Secretary of HHS has delegated to the Assistant Secretary for Health of HHS the authority to make domestic drug scheduling recommendations. 58 FR 35460 (July 1, 1993).
[2] 21 U.S.C. 811(d)(3).
[3] Id.
[4] 21 U.S.C. 811(d)(4)(A).

U.S.C. 811(a) and (b). Pursuant to 21 U.S.C. 811(a)(1), the Attorney General may, by rule, add to such a schedule or transfer between such schedules any drug or other substance, if he finds that such drug or other substance has a potential for abuse, and makes with respect to such drug or other substance the findings prescribed by 21 U.S.C. 812(b) for the schedule in which such drug or other substance is to be placed. The Attorney General has delegated this scheduling authority to the Administrator of the Drug Enforcement Administration (Administrator).[5]

Background

Zipeprol (chemical name: 1-methoxy-3-[4-(2-methoxy-2-phenylethyl)piperazin-1-yl]-1-phenylpropan-2-ol) is pharmacologically an opioid drug with some hallucinogenic properties that has no approved medical use in the United States.

In March 1995, the United Nations Commission on Narcotic Drugs, on the advice of the Director-General of the World Health Organization , placed zipeprol in Schedule II of the 1971 Convention, thus notifying all parties to the 1971 Convention.

DEA and HHS Eight Factor Analyses

On May 20, 2013, in accordance with 21 U.S.C. 811(b), and in response to the Drug Enforcement Administration's (DEA) August 3, 2009 request, HHS provided to DEA a scientific and medical evaluation and a scheduling recommendation for zipeprol. DEA subsequently reviewed HHS' evaluation and recommendation for schedule I placement and all other relevant data, and conducted its own analysis under the eight factors stipulated in 21 U.S.C. 811(c). DEA found, under 21 U.S.C. 812(b)(1), that this substance warrants control in schedule I. Both DEA and HHS analyses are available in their entirety under "Supporting and Related Material" of the public docket for this rule at *http://www.regulations.gov* under docket number DEA-477.

Notice of Proposed Rulemaking to Schedule Zipeprol

---

[5] 28 CFR 0.100.

On May 14, 2020, DEA published a notice of proposed rulemaking (NPRM) entitled "Schedules of Controlled Substances: Placement of zipeprol in schedule I."[6] The NPRM provided an opportunity for interested persons to file a request for a hearing in accordance with DEA regulations on or before June 15, 2020. No requests for such a hearing were received by DEA. The NPRM also provided an opportunity for interested persons to submit comments on the proposed rule on or before July 13, 2020.

Comments Received

DEA received eight comments on the proposed rule to control zipeprol in schedule I of the CSA.

Support for rulemaking

Comments: Three commenters recognized zipeprol's high potential for abuse and adverse health effects, including reports of hallucinations, seizures, overdoses, and deaths. Thus, these commenters supported the placement of zipeprol in schedule I.

DEA Response: DEA appreciates these comments in support of this rulemaking.

Dissent for rulemaking

Five commenters opposed the placement of zipeprol in schedule I, and provided various reasons as discussed below.

Comment: One commenter contended that it is not appropriate for DEA to schedule zipeprol as health experts, not law enforcement, should regulate and oversee all schedules I through III substances, and specifically that the Secretary of HHS is responsible for adding new substance to the CSA schedules.

DEA Response: DEA disagrees. Congress through the enactment of the CSA provided specific roles and procedures for both law enforcement (DEA) and the medical

[6] 85 FR 28899.

community (HHS) in controlled drugs with potential for abuse.[7] These procedures were followed in promulgating this final rule.

Comment: One commenter stated that all drugs need to be deregulated and decriminalized, and the focus of the law enforcement should be directed towards addressing social and non-drug related public health matters such as violent crime, unsolved murders, and control of obesity.

DEA Response: This comment is outside the scope of this rule insofar as it addresses drugs other than zipeprol. Regarding zipeprol, however, DEA maintains that control of zipeprol is needed and is appropriate. As stated in the background section, zipeprol is an opioid drug with some hallucinogenic properties that has no approved medical use in the United States.

In March 1995, the United Nations Commission on Narcotic Drugs, on the advice of the Director-General of the World Health Organization, placed zipeprol in Schedule II of the 1971 Convention, thus notifying all parties to the 1971 Convention. As a party to the 1971 Convention, the United States is taking action to place appropriate controls on zipeprol by scheduling it under the CSA.

Comment: One of two commenters mistakenly believe that zipeprol is a schedule II controlled substance under the CSA and that the proposed rule would reclassify zipeprol from schedule II to schedule I. The first commenter stated that reclassifying zipeprol to schedule I control does not warrant priority as it is not currently being used in the United States nor is it being actively manufactured or used in other countries, and there is a need for reclassification of many other drugs. This commenter added that marijuana needs to be reclassified from its current schedule I control.

DEA Response: DEA emphasizes to these commenters that zipeprol is not currently scheduled under the CSA. Perhaps the commenters are thinking of zipeprol's

[7] 21 U.S.C. 811(a) and (b).

control status under the 1971 Convention. As noted in the background section, the Committee on Narcotic Drugs added zipeprol to Schedule II of the 1971 Convention in March 1995. DEA further notes that classification of a drug under the 1971 Convention, and its relevant schedules, is different from that of the CSA.[8]

Regarding the comment about reclassifying marijuana, this current rulemaking pertains only to the scheduling of zipeprol. Therefore, this comment is outside the scope of this rule.

Comment: A commenter noted that zipeprol and dextromethorphan (DXM, unscheduled under the CSA) are both cough suppressants with potential for abuse; however, adding control of DXM should take priority over reclassifying control of zipeprol as DXM is available and "wildly abused" in the United States.

DEA Response: This current rulemaking pertains only to the scheduling of zipeprol. Therefore, this comment is outside the scope of this rule.

Comment: One commenter recognized zipeprol's high potential for abuse and dependence but expressed that zipeprol has an accepted medical use as a cough suppressant. The commenter noted that schedule I, by definition, is only for drugs with both no accepted medical use and a high potential for abuse. Therefore, the commenter contends that zipeprol should instead be placed in schedule II.

DEA Response: DEA does not agree. While zipeprol was previously marketed and used in other countries in the 1980s and 1990s as a cough suppressant (antitussive), hallucinations, convulsions, and opioid-like tolerance, along with both a psychological and physical dependence, have been reported following its ingestion. As discussed in

[8] The CSA has five schedules (schedules I–V) with specific criteria set forth for each schedule. Schedule I is the only possible schedule in which a drug or other substance may be placed if it has high potential for abuse and no currently accepted medical use in treatment in the United States. See 21 U.S.C. 812(b). In contrast, the 1971 Convention has four schedules (Schedules I–IV) but does not have specific criteria for each schedule. The 1971 Convention simply defines its four schedules, in Article 1, to mean the correspondingly numbered lists of psychotropic substances annexed to the Convention, and altered in accordance with Article 2.

HHS's eight-factor analysis, zipeprol is not approved by the Food and Drug Administration for use in the United States. As explained in the NPRM, the medical and scientific evaluation and scheduling recommendation issued by the Assistant Secretary for Health of HHS (Assistant Secretary for HHS) concludes that zipeprol has no currently accepted medical use in treatment in the United States, has high potential for abuse, and lacks accepted safety for use under medical supervision. Following DEA's proposed determination to place zipeprol in schedule I, as outlined in the NPRM, the Administrator maintains the appropriateness of that schedule placement and concludes that zipeprol warrants control in schedule I of the CSA.[9] Further, regarding the appropriateness of placing zipeprol in schedule I of the CSA, DEA notes that Article 2, paragraph 7(b), of the 1971 Convention sets forth the minimum requirements that the United States must meet when a substance has been added to Schedule II of the 1971 Convention. As a party to the 1971 Convention, the United States is taking action to place appropriate controls on zipeprol by scheduling it under the CSA.

DEA conducted an eight-factor analysis pursuant to 21 U.S.C. 811(c) and based its scheduling determination on a comprehensive evaluation of all available data. As stated in the NPRM, after careful review of all relevant data, DEA concurred with HHS' assessment that zipeprol has a high potential for abuse with no currently accepted medical use in treatment the United States and lacks accepted safety for use under medical supervision. Congress established only one schedule, schedule I, for drugs of abuse with "no currently accepted medical use in treatment in the United States" and "lack of accepted safety for use under medical supervision."[10] The other four schedules require the drug or other substance to have a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions (schedule

[9] 21 U.S.C. 812(b)(1).
[10] 21 U.S.C. 812(b).

II) or a currently accepted medical use in treatment in the United States (schedules III through V).[11] DEA is therefore promulgating this final rule placing zipeprol in schedule I under the CSA.

Scheduling Conclusion

After consideration of the public comments, the scientific and medical evaluation and accompanying recommendation of HHS, and conducting an independent eight-factor analysis, DEA finds substantial evidence of potential for abuse of zipeprol. As such, DEA is permanently scheduling zipeprol as a controlled substance under the CSA.

Determination of Appropriate Schedule

The CSA establishes five schedules of controlled substances known as schedules I, II, III, IV, and V.[12] The CSA also outlines the findings required to place a drug or other substance in any particular schedule.[13] After consideration of the analysis and recommendation of the Assistant Secretary for HHS and review of all other available data, the Administrator, pursuant to 21 U.S.C. 811(a) and 812(b)(1), finds that:

(1) Zipeprol has a high potential for abuse. This potential is comparable to certain schedule II substances (e.g., morphine);

(2) Zipeprol has no currently accepted medical use in treatment in the United States;[14] and

(3) There is a lack of accepted safety for use of zipeprol under medical supervision.

---

[11] Id.
[12] 21 U.S.C. 812(a).
[13] 21 U.S.C. 812(b).
[14] Although there is no evidence suggesting that zipeprol has a currently accepted medical use in treatment in the United States, it bears noting that a drug cannot be found to have such medical use unless DEA concludes that it satisfies a five-part test. Specifically, with respect to a drug that has not been approved by FDA, to have a currently accepted medical use in treatment in the United States, all of the following must be demonstrated: i. the drug's chemistry must be known and reproducible; ii. there must be adequate safety studies; iii. there must be adequate and well-controlled studies proving efficacy; iv. the drug must be accepted by qualified experts; and v. the scientific evidence must be widely available. 57 FR 10499 (1992), *pet. for rev. denied, Alliance for Cannabis Therapeutics v. DEA*, 15 F.3d 1131, 1135 (D.C. Cir. 1994).

Based on these findings, the Administrator concludes that zipeprol, including its isomers, esters, ethers, salts, and salts of isomers, esters and ethers, whenever the existence of such isomers, esters, ethers and salts is possible within the specific chemical designation, warrants control in schedule I of the CSA.[15]

Requirements for Handling Zipeprol

Effective as of [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER], zipeprol will be subject to the CSA's schedule I regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distribution, dispensing, importing, exporting, research, and conduct of instructional activities, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) zipeprol, or who desires to handle zipeprol, must be registered with DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. Any person who handles zipeprol and is not registered with DEA must submit an application for registration and may not continue to handle zipeprol after the effective date of this rule, unless DEA has approved that application, pursuant to 21 U.S.C. 822, 823, 957, and 958 and in accordance with 21 CFR parts 1301 and 1312.

2. *Disposal of stocks.* Any person unwilling or unable to obtain a schedule I registration must surrender all quantities of zipeprol as of the effective date of this rule, or may transfer all such quantities of currently held zipeprol to a person registered with DEA. Zipeprol is required to be disposed of in accordance with 21 CFR part 1317, in addition to all other applicable Federal, State, local, and tribal laws.

---

[15] 21 U.S.C. 812(b)(1).

3. *Security.* Zipeprol is subject to schedule I security requirements and must be handled and stored pursuant to 21 U.S.C. 821 and 823 and in accordance with 21 CFR parts 1301.71–1301.76. Non-practitioners handling zipeprol must also comply with the employee screening requirements of 21 CFR parts 1301.90-1301.93.

4. *Labeling and Packaging.* All labels, labeling, and packaging for commercial containers of zipeprol must comply with 21 U.S.C. 825, and be in accordance with 21 CFR part 1302.

5. *Quota.* Only registered manufacturers are permitted to manufacture zipeprol in accordance with a quota assigned pursuant to 21 U.S.C. 826 and in accordance with 21 CFR part 1303.

6. *Inventory*. Every DEA registrant who possesses any quantity of zipeprol must take an inventory of zipeprol on hand pursuant to 21 U.S.C. 827 and in accordance with 21 CFR parts 1304.03, 1304.04, and 1304.11(a) and (d).

Any person who registers with DEA must take an initial inventory of all stocks of controlled substances (including zipeprol) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827, 958, and in accordance with 21 CFR parts 1304.03, 1304.04, and 1304.11(a) and (b).

After the initial inventory, every DEA registrant must take an inventory of all controlled substances (including zipeprol) on hand every two years, pursuant to 21 U.S.C. 827, and in accordance with 21 CFR parts 1304.03, 1304.04, and 1304.11.

7. *Records and Reports.* Every DEA registrant must maintain records and submit reports with respect to zipeprol, pursuant to 21 U.S.C. 827, and in accordance with 21 CFR 1301.74(b) and (c), 1301.76(b), and parts 1304, 1312, and 1317. Manufacturers and distributors must submit reports regarding zipeprol to the Automation of Reports and Consolidated Order System pursuant to 21 U.S.C. 827 and in accordance with 21 CFR parts 1304 and 1312.

8. *Order Forms.* Every DEA registrant who distributes or orders zipeprol must comply with the order form requirements, pursuant to 21 U.S.C. 828 and in accordance with 21 CFR part 1305.

9. *Importation and Exportation.* All importation and exportation of zipeprol must comply with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312.

10. *Liability.* Any activity involving zipeprol not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Executive Orders 12866 (Regulatory Planning and Review) and 13563 (Improving Regulation and Regulatory Review)

In accordance with 21 U.S.C. 811(a), this final scheduling action is subject to formal rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget (OMB) pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of E.O. 13132. The rule does not have substantial direct effects on the States, on the relationship between the national government and the States, or the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination with Indian Tribal Governments

This rule does not have tribal implications warranting the application of E.O. 13175. It does not have substantial direct effects on one or more Indian tribes, on the

relationship between the Federal government and Indian tribes, or on the distribution of power and responsibilities between the Federal government and Indian tribes.

Regulatory Flexibility Act

The Administrator, in accordance with the Regulatory Flexibility Act, 5 U.S.C. 601–612, has reviewed this final rule and by approving it certifies that it will not have a significant economic impact on a substantial number of small entities.

DEA is placing the substance zipeprol, including its isomers, esters, ethers, salts, and salts of isomers, esters and ethers, whenever the existence of such isomers, esters, ethers and salts is possible within the specific chemical designation, in schedule I of the CSA. This action is being taken to enable the United States to meet its obligations under the 1971 Convention. This action imposes the regulatory controls and administrative, civil, and criminal sanctions applicable to schedule I controlled substances on persons who handle (manufacture, distribute, reverse distribute, import, export, engage in research, conduct instructional activities or chemical analysis with, or possess), or propose to handle zipeprol.

Based on the review of HHS' scientific and medical evaluation and all other relevant data, DEA determined that zipeprol has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and lacks accepted safety for use under medical supervision. DEA's research confirms that there is no legitimate commercial market for zipeprol in the United States. Therefore, DEA estimates that no United States entity currently handles zipeprol and does not expect any United States entity to handle zipeprol in the foreseeable future. DEA concludes that no legitimate United States entity would be affected by this rule. As such, this rule will not have a significant effect on a substantial number of small entities.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 *et seq.*, DEA has determined and certifies that this action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year * * *." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Congressional Review Act

This rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. However, pursuant to the CRA, DEA is submitting a copy of this final rule to both Houses of Congress and to the Comptroller General.

Signing Authority

This document of the Drug Enforcement Administration was signed on November 14, 2022, by Administrator Anne Milgram. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register Liaison Officer has been authorized to sign and submit the document in electronic format for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the Federal Register.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, 21 CFR part 1308 is amended as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

1. The authority citation for 21 CFR part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), 956(b), unless otherwise noted.

2. Amend § 1308.11 by adding paragraph (b)(92) to read as follows:

§ 1308.11 Schedule I.

* * * * *

(b) * * *

(92) Zipeprol (1-methoxy-3-[4-(2-methoxy-2-phenylethyl)piperazin-1-yl]-1-phenylpropan-2-ol)…….....9873

* * * * *

Scott Brinks
Federal Register Liaison Officer,
Drug Enforcement Administration

[FR Doc. 2022-25206 Filed: 11/18/2022 8:45 am; Publication Date: 11/21/2022]